DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study
PCOS Twin Study – Environmental factors in the development of polycystic ovary syndrome, Phase 2
IRB 9271-07-11R0

Why am I being asked to participate in this study?

You are being asked to participate in this research study because you are registered with the Mid Atlantic Twin Registry (MATR) and have previously indicated that you are interested in participating in research studies. You are also being asked to participate because you recently took a MATR phone survey on Polycystic Ovary Syndrome, or PCOS, and indicated in this survey that you have one or more traits that are associated with PCOS. Some of these traits are quite common, so having them does not mean that you have PCOS. PCOS can only be determined from a medical exam and blood testing.

Research studies include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

This study is sponsored by the Program in Clinical Research, National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH), Research Triangle Park, North Carolina in collaboration with the Duke University Medical Center. Drs. Patricia Chulada and Perry Blackshear from the NIEHS are the principal investigators of the study. Drs. Ann Brown and Tracy Setji are also study investigators and will be your doctors for the study.

What is the purpose of this study?

This study is Phase 2 of a multi-phase research study to identify the genetic and environmental risk factors for PCOS. The goal is to identify a group of female twin pairs in which one or both twins have PCOS. The data and clinical information collected during this study will be used to find out how much of PCOS is due to heredity (genes) and how much is due to environmental factors. This study may lead to future studies to identify what some of those genes and environmental factors are. Knowing what causes PCOS can help scientists develop new treatments and strategies for reducing a woman's chance of developing PCOS, especially if PCOS runs in her family. It might also lead to information on how to lower the rates of other conditions that are associated with PCOS such as obesity, diabetes, high cholesterol, high blood pressure, heart disease and certain cancers.

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How many subjects will participate in this study?

We are hoping to recruit as many twin pairs as possible. Our ultimate goal is 500 twin pairs.

What will happen if you take part in the study?

There are two parts to this study as described below.

1. Blood Test: For the first part of this study, you might be asked to provide a blood sample to test for the male hormone testosterone. Testosterone is generally present at low levels in all women, but is sometimes present at abnormally high levels in women with PCOS. If you are asked to have this test done at the beginning of the study, a home health care agent will come to your home (or workplace) to collect about one teaspoon of blood from your arm. We will pay for this test as well as all other costs associated with having the home health care agent come to your home to collect the blood sample. If your testosterone levels are normal, you do not meet the criteria for continued participation in the study at this time, but might be eligible at a later date. If your levels are above a certain level, you will be eligible to continue in the next part of the study.

2. Medical Evaluation: Based on the testosterone result and the results from the MATR PCOS survey you took previously, we may ask that both you and your twin sister travel to the Duke Clinical Research Unit (DCRU) at Duke University Medical Center (DUMC) in Durham, NC, for a medical examination to determine if you have PCOS. In this type of study, it is important that both members of a twin pair participate. Therefore, before your exam is scheduled, your twin sister must agree to participate, too.

The exam will be conducted by an endocrinologist, a doctor who specializes in PCOS and other hormone disorders. The full exam will take 4-6 hours and, depending on where you live, may require an overnight stay in Durham prior to the day of your appointment. We will make all the travel arrangements for you, and pay for all your travel expenses and meals, all the medical tests, and the exam itself. You will also be provided your test results when they are complete to take to your own doctor.

All the procedures you will undergo as part of this evaluation are described in detail below. Please review these procedures carefully before you decide to participate in this PCOS Twin Study.

Blood tests
During the morning of the medical exam, blood will be collected from you at three different time points. In preparation for these blood tests, you must not eat or drink anything (except water) after midnight the night before the exam. The exam will be scheduled for you early in the morning at Duke. Once you arrive at the clinic, lab personnel will collect the first set of blood samples (about 3 tablespoons or 1.5 ounces of blood) from your arm. This blood will be used to test for hormones and biochemical metabolites (products of various chemical processes of the body) as well as your baseline glucose (sugar) and insulin levels. It will also be used to perform a test to find out whether you and your sister are identical or fraternal twins. Finally, we will use the blood sample to test if you are pregnant. We are only doing a pregnancy test because if you are pregnant, this will affect your hormone levels and interfere with the data analyses for the study. You will be excluded from the study if we determine that you are pregnant, but you can continue with the exam for your own benefit if you wish. The exam and tests that will be performed will not harm you or your fetus.

Following this initial blood collection, you will drink approximately 1 cup (7.5 ounces) of a special cola drink (Glucola) that contains an exact amount (75 grams) of sugar. One and two hours later, clinic personnel will collect second and third blood samples (about 1 teaspoon) from your arm. After the third blood sample has been collected, the site coordinator will provide you with a light snack.

In between these blood draws and at other times during the day, you will undergo the procedures described below.

- ***Medical and Family History***: A doctor will ask you various questions about your personal and family medical history. It is important that you answer these questions honestly.

- ***Medical Exam***: A doctor will measure your weight, height, hip and waist circumference and your blood pressure, and will listen to your heart, chest and lungs. The doctor will also examine you for acanthosis nigricans. These are velvety, dark brown to black markings on the skin.
    - ***Stretch marks***: The doctor will examine you for stretch marks usually found around the abdomen
    - ***Androgen excess****:* The doctor will check you for baldness, acne, and excess hair growth. The latter will include the type and amount of hair on your lip, chin, chest, upper and lower back, upper and lower abdomen, thighs, legs and upper arms.
    - ***Ultrasound***: The most accurate method to tell whether or not you have cystic ovaries is to do a vaginal ultrasound. During this procedure a study sonographer or ultrasound technician will insert a long, thin cylindrical ultrasound transducer (probe) into your vagina. The technician will then gently move the transducer around in order to scan the ovaries. You may experience some mild discomfort due to the pressure of the probe. About 15-20% of the time, a vaginal ultrasound does not give a good picture of the ovaries. If this happens to you, you will also have an ultrasound done on your abdomen.
    - ***External genitalia examination:*** If necessary, you might be examined for an enlarged clitoris as this can indicate other conditions that act like PCOS.

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Optional future blood tests

If you give permission, during the medical evaluation, one tube of blood (about one tablespoon) will be collected and sent to a specimen repository at the NIEHS. Remaining blood components left over from other laboratory assays will also be sent to the same specimen repository at the NIEHS. At the repository, your blood will be stored in a freezer in a secure building indefinitely. There the sample will be labeled only with a unique personal identification number (PIN). The PIN key will be kept in a password protected file, on a computer system separate from your study data. Only personnel directly involved with this study will have access to the PIN key that links your identity to your blood sample and study results.

At a later date, we will use these specimens to measure certain hormones, vitamins, chemicals, other environmental agents, and measures of biological function. We also use your specimen to look at genes and gene products that could increase or decrease the risk of polycystic ovary syndrome. At this time, the specific type and number of tests we perform on your blood sample have not been determined. Based on the results, we might decode your PIN number so that we can identify you and invite you to participate in future voluntary research studies.

It is possible that this study will reveal information about you that was previously unknown (such as disease status or risk). Such incidental findings, if any, will not be shared with you or anyone related to you unless the incidental finding involves an inherited risk for a disease known at the time of testing to be likely to cause premature death if untreated. Should such life-threatening results be uncovered through these genetic research studies, and if they are directly applicable to you or to your minor children, you will be notified via certified mail to contact Dr. Chulada. Notification will be sent to the last address you provided to us. We will not release these specific research findings over the telephone or in the mail. Dr. Chulada will arrange for you to meet with her and/or a genetic counselor or other appropriate health care provider either at DUMC or another medical institution near your residence to review the research information.

May we collect this extra blood tube and blood left over from other assays and store it for possible future testing? (Please initial next to your choice.)

_____ I agree to have one extra tube of my blood stored for future testing.

_____ I DO NOT agree to have one extra tube of my blood stored for future testing.

_____ I agree to have blood leftover from other tests saved for possible future testing.

_____ I DO NOT agree to have blood leftover from other tests saved for possible future testing.

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Optional Skin Punch Biopsy

If you give permission, a skin punch biopsy will be taken from the underside of your upper arm that is 3 millimeters in diameter or about the size of a small pea. This skin biopsy will be used to culture cells that are called skin fibroblasts. These cells will be stored at the NIEHS and used for various tests that might include looking at the type and amount of proteins your cells produce or modifications to your DNA.

The procedure will only take about 10 minutes. First the doctor will disinfect the biopsy site with alcohol. Then she will inject a local anesthetic (lidocaine) into the site using a small needle and syringe. In very rare instances, people are allergic to lidocaine and can develop hives at the injection site. Therefore, if you have a history of allergic reactions to lidocaine, the doctor will not perform the biopsy. If you or someone in your immediate family has a history of keloid (large scar formation), the doctor will not perform the biopsy. Next a skin biopsy "punch" device will be inserted into the underside of your upper arm and then quickly removed. A "punch" is a special medical device used to remove a small circular piece of skin and can only penetrate the outer layer of skin or the epidermis. Once the punch has been removed, the doctor will place one dissolvable suture at the site to speed healing. This suture will absorb into your skin and ***will not*** need to be removed later by a doctor. Some scarring may occur and this will be visible as a small white dot on the inside of your upper arm.

Infection at the biopsy site is rare. You can prevent an infection from occurring by keeping the site clean and dry, and by applying the antibiotic ointment and bandages that are provided to you. If infection does occur, you should visit your local doctor or urgent care center for treatment and then contact the study coordinator. You will be reimbursed for all charges not covered by your insurance (co-pays, prescriptions, other). If you do not have insurance, you will be reimbursed for all charges incurred. If you decide to give a skin punch biopsy, you will receive an additional $50.

May we obtain a skin biopsy from you? (Please initial next to your choice.)

_____ I agree to give a skin punch biopsy.

_____ I DO NOT agree to give a skin punch biopsy.

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Optional exclusionary tests

Depending on the results of your exam and blood tests, there is a very small possibility that you have another condition that acts like PCOS. The study doctor may recommend that you have additional tests done after you leave Duke to rule out these conditions. These conditions are rare and the chances that you will be referred for extra testing are unlikely. But if you want, the study physician will discuss the tests with you and make arrangements for you to visit your own doctor or an endocrinologist closer to your home to have them done. If you decide to have these tests done, we will pay for them if you do not have insurance coverage for them. The two exclusionary tests are described below:

Dexamethasone suppression test

If you have symptoms of excessive cortisol (steroid) production (purplish stretch marks, easy bruising, weakness, rounded face or increased fat around the neck), the study doctor might recommend that you be tested for Cushing's Syndrome with a dexamethasone suppression test. For this test, you will need to take a dexamethasone pill at 11 PM one night, and then have your blood drawn at your local doctor's office at 8 AM the next morning. The blood sample will be tested for cortisol. If your cortisol level is normal the next morning, you probably DO NOT have Cushing's Syndrome and can continue in the PCOS Twin Study. However, if your cortisol level is increased the next morning, it's possible that you have Cushing's Syndrome. If this happens, you will no longer be eligible for this study. You should also discuss these results with your own doctor or endocrinologist. Risks of the dexamethasone suppression tests include bruising or slight pain where the blood is drawn. There is also a small possibility of an allergic reaction to the drug that might appear as hives, a skin rash and/or itching.

ACTH stimulation test

During your medical exam at Duke, we will test you for a condition called Non-Classical Congenital Adrenal Hyperplasia (NCCAH). If this test is abnormal, the study doctor might recommend that you have a ACTH stimulation test after you leave Duke. For this test, you will have your blood collected and then be injected with a hormone that stimulates your adrenal gland to produce hormones. After 60 minutes, a second blood sample will be collected and measured for an increase in 17-hydroxyprogesterone (a hormone that aids in diagnosing NCCAH). Risks of the ACTH Stimulation Test include minor irritation at the injection site (e.g. redness, swelling), or bruising or slight pain at the site of the blood collection. Rarely, individuals may experience dizziness, an irregular heartbeat, swelling, headache, or an allergic reaction to the medication. Since this test will be performed in the presence of medical personnel, any symptoms that you have will be responded to immediately.

_____ If the study doctor thinks I might have one of these rare conditions that acts like PCOS, I agree to consider having one of these other tests done. But, I am not required to have the test done if recommended.

_____ If the study doctor thinks I might have one of these rare conditions that acts like PCOS, I WILL NOT consider having one of these other tests done. The study physician shall not discuss them with me even if she thinks they would be useful.

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Testing for identical or fraternal twins

As part of this study, we will perform a genetic blood test to determine whether or not you and your twin are identical or fraternal twins. Some twins may not want this information so please indicate below if you would like to know which type of twins you are. Note that both you and your twin sister must agree to receive these results in order for you to receive them.

Would you like to know whether you are fraternal or identical twins? (Please initial next to your choice.)

_____ I agree to learn my zygosity results.

_____ I DO NOT agree to learn my zygosity results.

Providing data back to the Mid-Atlantic Twin Registry - Optional

We will give the MATR the results which tell us whether you are fraternal or identical twins. We will also give them any contact information changes you might have had since joining them. However, you can opt out of having us provide these data back to the MATR by initialing here.

May we provide your zygosity results and updated contact information to MATR? (Please initial next to your choice.)

_____ I agree to have my zygosity results and updated contact information provided to MATR.

_____ I DO NOT agree to have my zygosity results and updated contact information provided to MATR.

How long will your participation last?

If you are visited by the home health agent to draw the initial blood sample for bioavailable testosterone levels, it will take about one hour of your time. The amount of time it takes to complete the medical exam at Duke University Medical Center in Durham, NC will depend on where you live. If you are local to the Durham NC area, the exam may take 4-6 hours of your time. If you are not local and have to travel there the night before the exam, this might take about one and a half days of your time. Your participation in this study will end after the medical exam is complete.

What are the possible risks or discomforts?

Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely. During the transvaginal ultrasound, an ultrasound probe will be inserted into your vagina. You may feel some mild discomfort due to the pressure of the probe during this procedure. The transvaginal ultrasound may reveal findings that may cause anxiety and require further investigation by a gynecologist, such as a uterine lining biopsy or further imaging. If abnormal findings are noted, you will be referred to a gynecologist. The sponsor will not pay for these studies.

A skin punch biopsy is generally a non-hazardous procedure, but there are some risks such as: 1) an allergic reaction to the lidocaine (local anesthetic), 2) bleeding, 3) bruising, 4) infection and 5) scarring. In addition, you might have some soreness at the skin biopsy site once the local anesthetic wears off.

If the Duke physician recommends that you have extra tests done to rule out one of the conditions that mimics PCOS, there are small risks associated with those tests and they are described above. However, these conditions are very rare, and the chance that these tests will be recommended is very rare also.

What are the possible benefits?

You may not receive any direct benefit as a result of participating in this study. However, if you participate in the medical exam, you will receive diagnostic tests free of charge. These tests will not only tell you if you have PCOS, but will also tell you more about your general health as well, such as if you have diabetes, high blood pressure, high cholesterol and other conditions. You may also learn if you have another condition that mimics PCOS that you might not yet be aware of.

You will also indirectly benefit by helping scientists discover some of the genetic and environmental factors that can cause women to develop PCOS. The information from this and future studies will ultimately be used to develop strategies for preventing or treating PCOS in future women, and may help them lower their risks for other conditions such as obesity, diabetes, high cholesterol, high blood pressure, cardiovascular disease and certain cancers. If you are diagnosed with PCOS, you will not receive treatment for your PCOS as part of this study. We will refer you back to your own doctor for treatment or we will try to refer you to an appropriate doctor in your area.

If you choose not to participate, what other options do you have?

Your participation in this study is completely voluntary. If you chose to participate, you can withdraw at any time for any reason. Participating in this study does not mean that you are obligated to participate in future studies if asked.

The alternative to participating is that you do nothing or have your own doctor examine you for the symptoms you reported, if any, on the earlier PCOS phone survey.

What if we learn about new risks during the study?

The goal of this phase of the study is only to identify twin pairs in which one or both co-twins have PCOS. Therefore, it is unlikely that we will learn about any new risks for PCOS in this phase of the study. We will give you all your test results. If you are diagnosed with PCOS or one of the secondary PCOS conditions as part of this study, you will be encouraged to follow up with your personal doctor. Even if test results do not indicate PCOS, they may indicate another condition that you should have evaluated.

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How will your privacy be protected?

Every effort will be made to protect your identity and study results consistent with laws relating to public disclosure of health information. Upon your arrival at Duke, you will be assigned a Duke Medical Records Number and hard copies of your medical evaluation results will be maintained in a medical records folder, following Duke Healthcare medical records procedures.

Data kept by the study investigators will be coded with a personal identification number. The key to this code and study data will be stored in password-protected electronic files and back-up disks will be stored in locked cabinets. Hard copies of study data will be stored in locked filing cabinets. Only the investigators and personnel directly involved in this study will have access to the key to your personal information and your study data. Also, your test results will not be shared with your twin.

All data and samples are the property of the National Institute of Environmental Health Sciences (NIEHS), a Center of the National Institutes of Health, and can only be obtained by unaffiliated persons through legal process or court order. Because this study is sponsored by the NIEHS, it falls under the Federal Privacy Act which protects the confidentiality of your data and medical records. However, you should know that the Act allows release of some information from your research and/or medical records without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

What will happen to the blood samples you give?

The blood left over from your medical exam will be discarded once the tests are complete. If you agreed to give an extra sample for future testing, it will be coded and kept in a repository indefinitely. If you want this specimen removed from the repository at any time, we ask that you contact Ms. Linville in writing at the address below and let her know that you want the sample removed and destroyed. Once we receive your letter, we will discard what blood or DNA samples are remaining so that it cannot be used for future analyses. If your blood has already been analyzed for various metabolites or genetic tests and the data have been statistically analyzed, we will not be able to remove the data from our databases, but you will never be identified personally.

Will you be paid for participating?

You will be paid $25 if you give the initial blood sample for your testosterone level. You will be paid $100 if you undergo the medical exam at Duke University in Durham, NC or at another clinic. You will also be paid an additional $50 if you decide to give a skin biopsy.

Will it cost you anything to participate?

Other than your time, there will be no cost to you for participating in this study.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time for any reason. If you withdraw from the study, no new data about you will be collected for study purposes. In this case, the study doctors at Duke will send all data that have already been collected for study purposes to you or your personal doctor.

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Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact the Study Coordinator, Julie Linville, in writing and let her know that you are withdrawing from the study. Ms. Linville's mailing address is:

Julie Linville
Constella Group, LLC
2605 Meridian Parkway, Ste 200
Durham, NC 27713

What if I am injured as a result of my participation in this study?

Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of participating in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

If you believe that you have been injured as a result of participating in this study, contact Pat Chulada at 919-541-7736 who will help you to obtain appropriate medical care. Any costs of treatment should be billed to your insurance company. You will be reimbursed for expenses for short term care that is not covered by your insurance, or in full if you do not have insurance, e.g. infection from the skin biopsy. However, no long-term medical care or financial compensation for research-related injuries will be provided by the NIEHS, the NIH, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have further questions, you should contact the Study Coordinator, Julie Linville, at 866-809-1260.

What if you have questions about your rights as a subject?

For questions about your rights as a research participant, contact the following individuals:

- For the **NIEHS Institutional Review Board** (IRB), please call **Dr. Marian Johnson-Thompson**, NIEHS IRB Chairperson, at 919-541-4265
- For the **Duke University Health System IRB**, please call 919-668-5111.

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Subject's Agreement:

"The purpose of this study, the procedures to be followed, risks, and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have additional questions. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed copy of this consent form."

Signature of Research Subject | Date

Printed Name of Research Subject

Signature of Person Verifying or Witnessing Research Subject Signature | Date

Printed Name of Person Verifying or Witnessing Research Subject Signature